other than $pRB^{94}$ or $pRB^{56}$, in which said modified retinoblastoma tumor suppressor protein comprises an insertion, substitution or deletion within the N-terminal 378 amino acids of said protein, with the proviso that said modified protein does not consist of a deletion or substitution of amino acids 184-192 or 245-262, which modified retinoblastoma protein has a biological activity at least equivalent to the biological activity of the corresponding wild type retinoblastoma protein.

## REMARKS

Upon entry of this Reply, claims 1-32, 36, 37 and 44-48 will be pending and under active consideration.

Claims 1 and 36 have been amended to more particularly point out and distinctly claim the subject matter of the invention. Specifically, claims 1 and 36 have been amended to recite that the isolated gene encodes a modified retinoblastoma tumor suppressor protein other than $pRB^{94}$ or $pRB^{56}$, in which said modified retinoblastoma tumor suppressor protein comprises an insertion, substitution or deletion within the N-terminal 378 amino acids of said protein, with the proviso that said modified protein does not consist of a deletion or substitution of amino acids 184-192 or 245-262, which modified retinoblastoma protein has a biological activity at least equivalent to the biological activity of the corresponding wild type retinoblastoma protein. Support for this amendment is found throughout the specification as filed, specifically, *inter alia*, at page 6, lines 28-30; page 7, line 6 to page 8, lines 26; and page 10, lines 25-30.

Support for the proposition that claims can be properly amended or drafted to exclude a particular species of a genus can be found in *In re Johnson*, 194 U.S.P.Q. 187 (C.C.P.A. 1977). There the court considered the sufficiency under 35 U.S.C. § 112 of a specification in which a genus and several species were disclosed. The applicant claimed the genus while excluding two of the disclosed species in order to avoid the prior invention of another. The court reversed the decision of the Patent and Trademark Office Board of Appeals and held that an application which discloses a genus and several species provides sufficient support under Section 112 for claims excluding certain species in order to avoid a prior art rejection.

No new matter is added by the amendments to the claims.

1. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

A. Claims 1-34 and 36-37 are rejected under 35 U.S.C. § 112, first paragraph, allegedly, for containing subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the art that the inventor(s), at the time the invention was filed, had possession of the claimed invention. Specifically, the Examiner alleges that claims 1 and 36 contain new matter for reciting "with the proviso that said modified protein does not comprise a deletion of amino acids 1 through 378".

Applicants respectfully disagree with respect to the claims as amended, and point out that in order to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, an Applicant "must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). For purposes of a 'written description' inquiry, whatever is now claimed by Applicants constitutes the invention. See *Vas-Cath* at page 1117.

Applicants point out that claims 1 and 36 have been amended such that the objected proviso has been deleted. Applicants note that the proviso was redundant since a deletion of 378 amino acids is equivalent to $pRB^{56}$, which $pRB^{56}$ is already excluded from the claimed subject matter. See the specification at page 7, lines 2-4, which explains that $pRb^{56}$ has the N-terminal 379 contiguous amino acids deleted as compared to wild-type pRb. Applicants note, however, that claims 1 and 36, as amended herein, recite another proviso. Applicants note that such a proviso to exclude certain prior art compounds meets Section 112, first paragraph, requirements. See above regarding the discussion of *In re Johnson*.

B. Claims 31-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner alleges that the specification as filed is not enabling for gene therapy because the art of gene therapy is highly unpredictable. Applicants respectfully disagree.

Under 35 U.S.C. § 112, a patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless the Patent and Trademark Office provides sufficient reason to doubt the accuracy of the disclosure. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 U.S.P.Q. 367, 369-70 (CCPA 1971). The claimed

invention disclosed in the specification cannot be questioned on the unsupported skepticism of the Examiner. *Ex parte Linn*, 123 U.S.P.Q. 262 (PTO Bd. Pt. App. Int. 1959); *Ex parte Rosenwald*, 123 U.S.P.Q. 261 (PTO Bd. Pt. App. Int. 1959) (emphasis added). The number and variety of examples is irrelevant if the disclosure is "enabling" and set forth the "best mode contemplated." There is no absolute statutory requirement for a working example if the disclosure is such that one skilled in the art can practice the claimed invention. *In re Borkowski et al.*, 164 U.S.P.Q. 642 (CCPA 1970) (emphasis added). Even in an unpredictable art, Section 112 does not require disclosure of a test of every species encompassed by the claims. *In re Angstadt*, 190 U.S.P.Q. 214, 218 (CCPA 1976). An invention is enabled even though the disclosure may require some routine experimentation to practice the invention. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The fact that the required experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). A considerable amount of experimentation is permitted if it is merely routine or the specification provides a reasonable amount of guidance and direction to the experimentation. *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988); *In re Jackson*, 217 USPQ 804, 807 (PTO Bd. Pt. App. Int. 1982) (emphasis added). Finally, the Examiner has the burden of showing that the disclosure entails undue experimentation. *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (CCPA 1976) (emphasis added).

Here, the specification provides considerable guidance and direction to practice the claimed invention. The Examiner's attention is invited the specification at page 16, lines 11-18 which states:

> The invention also provides a recombinant host cell comprising a DNA segment comprising an isolated gene encoding a modified retinoblastoma tumor suppressor protein other than $pRB^{94}$, the modified retinoblastoma tumor suppressor protein comprising an N-terminal modification. In one aspect of the invention the host cell is a prokaryotic host cell. In another aspect of the invention the host cell is *E. coli*. In a further aspect of the invention the host cell is a eukaryotic host cell. In yet another aspect of the invention the host cell is a tumor cell. In still another aspect of the invention the DNA segment is introduced into the cell by means of a recombinant vector.

The specification also describes on page 21, line 7 to page 27, line 20 that retinoblastoma is a tumor suppressor gene and has tumor growth suppressive activity, and on page 30, line 1 to

page 43, line 12 teaches recombinant vectors comprising nucleic acids encoding the modified retinoblastoma protein and methods for delivering the vector into host cells. Moreover, the specification at page 23, line 7 *et seq.* teaches pharmaceutical compositions and routes of administration of the compositions into an organism.

Further, the specification describes in detail in Examples 1 through 10 of the production of exemplary vectors encoding for a modified retinoblastoma protein and transformation of host cells with said vectors. Moreover, the specification in Example 11 describes how therapeutic administration of the vectors encoding for a modified retinoblastoma protein of the present invention into subjects with tumors can be performed. The specification clearly enables one of skill in the art to practice the full scope of the claimed methods.

An invention meets the standard for successful practice set by Section 112 unless the invention is "totally incapable of achieving a useful result." *Brooktree v. Advances Micro Devices*, 24 U.S.P.Q.2D 1401, 1412 (Fed. Cir. 1992). The Examiner's attention is directed to the opinion of the Court of Appeals for the Federal Circuit (Federal Circuit) in *In re Brana*, 34 U.S.P.Q.2d 1437 (Fed. Cir. 1995). In *Brana*, the Board had affirmed a final rejection under Section 112, 1st paragraph, of claims covering certain compounds asserted to be useful as anti-tumor substances because it was alleged that the specification was non-enabling since it did not sufficiently establish that the claimed compounds had a practical utility, *i.e.*, as anti-tumor agents. 34 U.S.P.Q.2d at 1439.

The Federal Circuit emphatically reversed the Board's decision. First, it explained the legal standard for compliance with the relevant Section 112 requirement, explaining that "unless there is reason to doubt the objective truth of the statements contained [in the specification] which must be relied on for enabling support", a specification's disclosure "must be taken as in compliance with the enabling requirement." *Id.* at 1441 (emphasis in the original). Further, the *Brana* Court made clear that the Patent and Trademark Office has the initial burden of challenging a presumptively correct assertion of utility; evidence must be presented that those of skill in the art would doubt the disclosure. Only then must the applicant provide rebuttal evidence.

Second, the Federal Circuit explained that even if one of skill in the art would have questioned the asserted utility, all applicants need do to overcome the rejection is to

proffer sufficient evidence to convince one skilled in the art of the asserted utility. *Id.* at 1441.

In the *Brana* situation, the Court found that the Patent and Trademark Office had not met its initial burden. Further, the Court held that even if the Patent and Trademark Office had met its burden, the evidence proffered was clearly sufficient to meet the statutory requirement. As explained by the Court:

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.*Id.* at 1442 [quoting *In re Krimmel*, 292 F.2d 948, 953 (CCPA 1961)].

The Federal Circuit further reminded the Commissioner that testing for the full safety and effectiveness of a product is more properly left to the Food and Drug Administration and the requirements under the law for obtaining a patent should not be confused with the requirements for obtaining government approval to market a particular drug for consumption. *Id.* at 1442; *see*, *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994).

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *Id.*

While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

*Id.* at 219 (emphasis in the original).

In view of the above remarks, it is submitted that the specification provides sufficient teaching to allow one skilled in the art to successfully make and use the claimed recombinant host cells expressing a modified retinoblastoma tumor suppressor protein, without undue experimentation. This rejection under Section 112, first paragraph, therefore, should be withdrawn.

2. REJECTION UNDER 35 U.S.C. § 102

Claims 1, 2, 8, 20, 23, 24, 27, 28-30, 34, 36 and 37 are rejected under 35 U.S.C. 102(b), allegedly, as anticipated by U.S. Patent No. 5,969,120 to Fung ("Fung"). According to the Examiner, the invention of claims 1, 2, 8, 20, 23, 24, 27-30, 34, 36 and 37 is anticipated by Fung since Fung discloses mutants of pRb at amino acid positions 184, 186, 188, 189 and 191, which mutants have biological activity in being able to inhibit cell growth.

Applicants respectfully disagree with the Examiner. The present invention is directed to modified DNA segment comprising an isolated gene encoding a modified retinoblastoma protein other than $pRB^{94}$ or $pRB^{56}$, in which said modified retinoblastoma tumor suppressor protein comprises an insertion, substitution or deletion within the N-terminal 378 amino acids of said protein, with the proviso that said modified protein does not consist of a deletion or substitution of amino acids 184-192 or 245-262, which modified retinoblastoma protein has a biological activity at least equivalent to the biological activity of the corresponding wild type retinoblastoma protein. Fung discloses mutating conserved amino acid residues 184, 186, 188, 189 and 191[1], and Fung discloses that each of the mutants retained cell growth suppression activity.

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[1] Note that Fung does not disclose exactly how the amino acids are mutated, *i.e.*, Fung does not disclose whether the amino acid residues were substituted with another residue or whether the particular amino acids were deleted.

In order for a reference to anticipate a claim, each and every element of the claim must be disclosed in that one reference. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565 (Fed. Cir. 1985). "Anticipation under Section 102 can be found only if a reference shows exactly what is claimed . . ." Structural Rubber Prod. Co. v. Park Rubber Co., 749 F.2d 707 (Fed. Cir. 1984). Fung cannot and does not anticipate the claimed nucleic and amino acid sequences since Fung does not teach a DNA segment comprising an isolated gene encoding a modified retinoblastoma protein other than $pRB^{94}$ or $pRB^{56}$, in which said modified retinoblastoma tumor suppressor protein comprises an insertion, substitution or deletion within the N-terminal 378 amino acids of said protein, with the proviso that said modified protein does not consist of a deletion or substitution of amino acids 184-192 or 245-262, which modified retinoblastoma protein has a biological activity at least equivalent to the biological activity of the corresponding wild type retinoblastoma protein.

Moreover, Applicants note that the currently pending claims require that the biological activity of the modified Rb protein is at least equivalent to the wild-type Rb protein. Fung does not teach, which, if any, of the mutated Rb proteins has cell growth suppression activity at least equivalent to wild-type Rb. Thus, Feng does not anticipate the claimed invention since Feng does not teach that the mutant Rb proteins at amino acid positions 184, 186, 188, 189 and 191 have biological activity at least equivalent to wild-type.

Applicants respectfully submit that Fung does not anticipate the presently pending claims, and thus, withdrawal of this Section 102 rejection is respectfully requested.

3. REJECTION UNDER 35 U.S.C. § 103

Claims 1, 2, 8, 10, 13, 16, 20-22, 23-30, 34, 36, and 44-46 are rejected under 35 U.S.C. 103(a), allegedly, as obvious over U.S. Patent No. 5,969,120 to Fung ("Fung"), in view of European Patent Publication EP 0 259 031 to Dryja et al., published March 9, 1988 ("Dryja") and Friend et al., 1987, Proc. Natl. Acad. Sci. USA 84:9059-9063 ("Friend"). According to the Examiner:

> It would have been obvious to one of ordinary skill in the art at the time of the claimed invention to make deletions in the N-terminal region of RB using the DNA taught by Dryja or Friend et al., make vectors and study their effect on the growth of transformed cells with a reasonable expectation of success. An artisan would have been motivated to delete parts of the N-terminus of RB sequentially because it has phosphorylation sites that may be relevant to RB function and also because it has regions that, though are not located in the known DNA binding domains, are important for function (as

taught by Fung in columns 11 ans 12). Regarding the vectors of claims 25 and 26, it is noted that it would have been obvious to make adenoviral vectors or adenovirus comprising the deletion mutants of RB because these vectors allow expression of the mutant RB proteins in vivo (see lines 61-67 in column 8 and lines 1-16 in column 9 of Fung).

Applicants respectfully disagree with the Examiner's rejection. Fung discloses mutating conserved amino acid residues 184, 186, 188, 189 and 191, and that each of the mutants retained cell growth suppression activity. Dryja teaches a retinoblastoma protein in which the first 112 amino acids have been deleted as compared to wild type retinoblastoma, called $pRB^{94}$. Friend teaches deletion of DNA sequences in retinoblastomas and mesenchymal tumors, which sequences correspond to the deletions in the retinoblastoma gene locus.

A rejection for obviousness is improper when there is nothing in the cited prior art references, either singly or in combination, to suggest the desirability of the claimed subject matter. For a rejection of claimed subject matter as obvious in view of a combination of prior art references to be upheld, the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or use the claimed method, as the case may be; and the prior art must have revealed that in so doing, those of ordinary skill would have had a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). The claimed subject matter is directed to a DNA segment comprising an isolated gene encoding a modified retinoblastoma tumor suppressor protein other than $pRB^{94}$ or $pRB^{56}$, in which said modified retinoblastoma tumor suppressor protein comprises an insertion, substitution or deletion within the N-terminal 378 amino acids of said protein, with the proviso that said modified protein does not consist of [comprise] a deletion or substitution of amino acids 184-192 or 245-262 [1 through 378], which modified retinoblastoma protein has a biological activity at least equivalent to the biological activity of the corresponding wild type retinoblastoma protein. Applicants note that the claim requires that there be an insertion, substitution or deletion in the modified protein and that the modified protein have biological activity at least equivalent to the wild-type protein.

None of the cited references disclose that the modified proteins has a biological activity at least equivalent to the corresponding wild-type protein. Fund discloses

that modified Rb proteins have activity but not whether such activity is equivalent to wild-type. Dryja discloses a protein which is explicitly excluded from the claimed subject matter and Friend also does not disclose activity of the proteins, in fact since the proteins correspond to those in tumor cells, one skilled in the art might conclude that they were actually inactive.

Applicants respectfully submit that the Examiner seems to stating no more than it would have been obvious to try to make N-terminal mutations in the Rb gene to produce modified proteins having a biological activity at least equivalent to the wild-type Rb protein. An obvious to try standard is not a legally sufficient basis to sustain a rejection under 35 U.S.C. § 103. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). "[The Court of Appeals for the Federal Circuit has] consistently held that obvious to try is not to be equated with obviousness under 35 U.S.C. § 103." *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923 (Fed. Cir. 1990). "[T]his is not the standard of 35 U.S.C. § 103". *In re Geiger*, 2 USPQ2d 1276 (Fed. Cir. 1987). Applicants, therefore, respectfully submit that the Examiner has not met his burden in setting forth a *prima facie* case of obviousness and as such the rejection, based on 35 U.S.C. §103 for obviousness, should be withdrawn.

In view of the foregoing, Applicants submit that none of the cited references, either alone or in combination, renders obvious the claimed subject matter, and thus, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103.

## CONCLUSION

Applicants respectfully request that the amendments and remarks of the present response be entered and made of record in the file of the above-identified patent application. Claims 1-32, 36, 37 and 44-48 fully meet all statutory requirements for patentability. Withdrawal of the Examiner's rejections, allowance and action for issuance are respectfully requested.

Applicants respectfully request that the Examiner call the undersigned at (212) 790-9090 if any questions or issues remain.

Respectfully submitted,

Date June 28, 2001

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Enclosures

# EXHIBIT A

Serial No. 09/026,459
Filed February 19, 1998
Attorney Docket No. 8660-025

**MARKED-UP VERSION OF CLAIMS**
**UNDERLINED TEXT IS ADDED AND [BRACKETED TEXT] IS DELETED**

1 (twice amended). A DNA segment comprising an isolated gene encoding a modified retinoblastoma tumor suppressor protein other than $pRB^{94}$ or $pRB^{56}$, in which said modified retinoblastoma tumor suppressor protein comprises an insertion, substitution or deletion within the N-terminal 378 amino acids of said protein, with the proviso that said modified protein does not consist of [comprise] a deletion or substitution of amino acids 184-192 or 245-262 [1 through 378], which modified retinoblastoma protein has a biological activity at least equivalent to the biological activity of the corresponding wild type retinoblastoma protein.

36 (twice amended). A recombinant host cell comprising a DNA segment comprising an isolated gene encoding a modified retinoblastoma tumor suppressor protein other than $pRB^{94}$ or $pRB^{56}$, in which said modified retinoblastoma tumor suppressor protein comprises an insertion, substitution or deletion within the N-terminal 378 amino acids of said protein, with the proviso that said modified protein does not consist of [comprise] a deletion or substitution of amino acids 184-192 or 245-262 [1 through 378], which modified retinoblastoma protein has a biological activity at least equivalent to the biological activity of the corresponding wild type retinoblastoma protein.